NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF COCONUT OIL ACID DIETHANOLAMINE CONDENSATE

(CAS NO. 68603-42-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(DERMAL STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

January 2001

NTP TR 479

NIH Publication No. 01-3969

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Details about ongoing and completed NTP studies are available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov. Abstracts of all NTP Technical Reports and full versions of the most recent reports and other publications are available from the NIEHS' Environmental Health Information Service (EHIS) http://ehis.niehs.nih.gov (800-315-3010 or 919-541-3841). In addition, printed copies of these reports are available from EHIS as supplies last. A listing of all the NTP reports printed since 1982 appears on the inside back cover.

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF COCONUT OIL ACID DIETHANOLAMINE CONDENSATE

(CAS NO. 68603-42-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(DERMAL STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

January 2001

NTP TR 479

NIH Publication No. 01-3969

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

CONTRIBUTORS

National Toxicology Program
Evaluated and interpreted results and reported findings

R.D. Irwin, Ph.D., Study Scientist
D.A. Bridge, B.S.
J.R. Bucher, Ph.D.
R.E. Chapin, Ph.D.
J.R. Hailey, D.V.M.
J.K. Haseman, Ph.D.
J.R. Leininger, D.V.M., Ph.D.
R.R. Maronpot, D.V.M.
D.P. Orzech, M.S.
G.N. Rao, D.V.M., Ph.D.
J.H. Roycroft, Ph.D.
C.S. Smith, Ph.D.
G.S. Travlos, D.V.M.
D.B. Walters, Ph.D.
K.L. Witt, M.S., Integrated Laboratory Systems, Inc.

Battelle Columbus Laboratories
Conducted studies, evaluated pathology findings

P.J. Kurtz, Ph.D., Principal Investigator
(14-week and 2-year studies)
M.R. Hejtmancik, Ph.D., Principal Investigator
(2-year studies)
J.D. Toft II, D.V.M., M.S. (14-week and 2-year rats)
M.J. Ryan, D.V.M., Ph.D. (14-week mice)
A.W. Singer, D.V.M. (2-year mice)

Experimental Pathology Laboratories, Inc.
Provided pathology quality assurance

J.F. Hardisty, D.V.M., Principal Investigator
S. Botts, M.S., D.V.M., Ph.D.
P. Mann, D.V.M.

Dynamac Corporation
Prepared quality assurance audits

S. Brecher, Ph.D., Principal Investigator

NTP Pathology Working Group
Evaluated slides, prepared pathology report on rats (27 March 1997)

M. Butt, D.V.M., Chairperson
Pathology Associates International
J.R. Hailey, D.V.M.
National Toxicology Program
J.R. Leininger, D.V.M., Ph.D.
National Toxicology Program
P. Mann, D.V.M.
Experimental Pathology Laboratories, Inc.
R. Miller, D.V.M., Ph.D.
North Carolina State University
A. Radovsky, D.V.M., Ph.D.
National Toxicology Program

Evaluated slides, prepared pathology report on mice (8 May 1997)

M. Butt, D.V.M., Chairperson
Pathology Associates International
S. Botts, M.S., D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
J.R. Hailey, D.V.M.
National Toxicology Program
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
J.R. Leininger, D.V.M., Ph.D.
National Toxicology Program
R. Miller, D.V.M., Ph.D.
North Carolina State University
A. Yoshida, D.V.M., Ph.D., Observer
National Toxicology Program

Analytical Sciences, Inc.
Provided statistical analyses

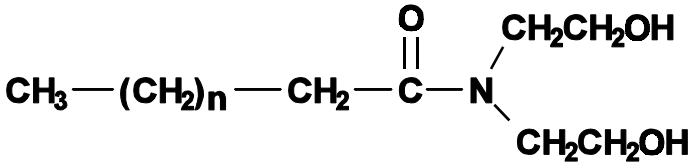
R.W. Morris, M.S., Principal Investigator
S.R. Lloyd, M.S.
N.G. Mintz, B.S.

Biotechnical Services, Inc.
Prepared Technical Report

S.R. Gunnels, M.A., Principal Investigator
J.R. Dias, M.S.
L.M. Harper, B.S.
A.M. Macri-Hanson, M.A., M.F.A.
D.P. Shaw, B.A.

CONTENTS

ABSTRACT



n = 7, 9, 11, 13, or 15

COCONUT OIL ACID DIETHANOLAMINE CONDENSATE

CAS No. 68603-42-9

Chemical Formula: $C_{(7+n)}H_{(15+2n)}O_3N$ Molecular Weight: 280-290

Synonyms: Cocamide DEA; cocamide diethanolamine; coconut oil diethanolamine; N,N-bis(hydroxyethyl)coco amides; N,N-bis(hydroxyethyl)coco fatty amides

Trade names: Clindrol 200CGN; Clindrol 202CGN; Clindrol Superamide 100CG; Comperlan KD; Comperlan LS; Comperlan PD; Conco Emulsifier K; Elromid KD 80; Empilan CDE; Ethylan LD; Ethylan A 15; Lauridit KDG; Marlamid D 1218; Monamid 150D; Monamid 150DB; Ninol 1281; Ninol 2012E; Ninol 2012 Extra; Ninol P 621; P and G Amide 72; Purton CFD; Schercomid CDA; Steinamid DC 2129; Steinamid DC 2129E; Varamide A 2; Varamide A 10; Varamide A 83; Witcamide 82; Witcamide 5133

Coconut oil acid diethanolamine condensate, a mixture of fatty acid diethanolamides of the acids found in coconut oil, is widely used in cosmetics, shampoos, soaps, and related consumer products. Because of the lack of information about potential risks associated with long-term exposure, coconut oil acid diethanolamine condensate was selected as a representative of the diethanolamine chemical class for evaluation of toxicity and carcinogenic potential.

Male and female F344/N rats and B6C3F$_1$ mice received dermal applications of coconut oil acid diethanolamine condensate for 14 weeks or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, L5178Y mouse lymphoma cells, cultured Chinese hamster ovary cells, and mouse peripheral blood erythrocytes.

14-WEEK STUDY IN RATS

Groups of 10 male and 10 female F344/N rats received dermal applications of 0, 25, 50, 100, 200, or 400 mg coconut oil acid diethanolamine condensate/kg body weight in ethanol, five times per week for 14 weeks. All rats survived until the end of the study. Final mean body weights and body weight gains of 200 and 400 mg/kg males and females were significantly less than those of the vehicle controls. Clinical findings included irritation of the skin at the site of application in 100, 200, and 400 mg/kg males and females. Cholesterol concentrations were significantly decreased in 200 and 400 mg/kg males and in females administered 100 mg/kg or greater; triglyceride concentrations were also decreased in 200 and 400 mg/kg males. Histopathologic lesions of the skin at the site of application included epidermal

hyperplasia, sebaceous gland hyperplasia, chronic active inflammation, parakeratosis, and ulcer. The incidences and severities of these skin lesions generally increased with increasing dose in males and females. The incidences of renal tubule regeneration in 100, 200, and 400 mg/kg females were significantly greater than the vehicle control incidence, and the severities in 200 and 400 mg/kg females were increased.

14-Week Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice received dermal applications of 0, 50, 100, 200, 400, or 800 mg coconut oil acid diethanolamine condensate/kg body weight in ethanol, five times per week for 14 weeks. All mice survived until the end of the study. Final mean body weights and body weight gains of dosed males and females were similar to those of the vehicle controls. The only treatment-related clinical finding was irritation of the skin at the site of application in males and females administered 800 mg/kg. Weights of the liver and kidney of 800 mg/kg males and females, the liver of 400 mg/kg females, and the lung of 800 mg/kg females were significantly increased compared to the vehicle controls. Epididymal spermatozoal concentration was significantly increased in 800 mg/kg males. Histopathologic lesions of the skin at the site of application included epidermal hyperplasia, sebaceous gland hyperplasia, chronic active inflammation, parakeratosis, and ulcer. The incidences and severities of these skin lesions generally increased with increasing dose in males and females.

2-Year Study in Rats

Groups of 50 male and 50 female F344/N rats received dermal applications of 0, 50, or 100 mg coconut oil acid diethanolamine condensate/kg body weight in ethanol five times a week for 104 weeks.

Survival, Body Weights, and Clinical Findings

The survival rates of treated male and female rats were similar to those of the vehicle controls. The mean body weights of dosed males and females were similar to those of the vehicle controls throughout most of the study. The only chemical-related clinical finding was irritation of the skin at the site of application in 100 mg/kg females.

Pathology Findings

There were marginal increases in the incidences of renal tubule adenoma or carcinoma (combined) in 50 mg/kg females. The severity of nephropathy increased with increasing dose in female rats. Non-neoplastic lesions of the skin at the site of application included epidermal hyperplasia, sebaceous gland hyperplasia, parakeratosis, and hyperkeratosis, and the incidences and severities of these lesions increased with increasing dose. The incidences of chronic active inflammation, epithelial hyperplasia, and epithelial ulcer of the forestomach increased with dose in female rats, and the increases were significant in the 100 mg/kg group.

2-Year Study in Mice

Groups of 50 male and 50 female B6C3F$_1$ mice received dermal applications of 0, 100, or 200 mg coconut oil acid diethanolamine condensate/kg body weight in ethanol five times a week for 104 to 105 weeks.

Survival, Body Weights, and Clinical Findings

Survival of dosed male and female mice was generally similar to that of the vehicle controls. Mean body weights of 100 mg/kg females from week 93 and 200 mg/kg females from week 77 were less than those of the vehicle controls. The only clinical finding attributed to treatment was irritation of the skin at the site of application in males administered 200 mg/kg.

Pathology Findings

The incidences of hepatic neoplasms (hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma) were significantly increased in male and/or female mice. Most of the incidences exceeded the historical control ranges. The incidences of eosinophilic foci in dosed groups of male mice were increased relative to that in the vehicle controls.

The incidences of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) were significantly increased in 200 mg/kg males.

Several nonneoplastic lesions of the skin at the site of application were considered treatment related. Incidences of epidermal hyperplasia, sebaceous gland hyperplasia, and hyperkeratosis were greater in all dosed groups of males and females than in the vehicle controls. The incidences of ulcer in 200 mg/kg males and inflammation and parakeratosis in 200 mg/kg females were greater than those in the vehicle controls.

The incidences of thyroid gland follicular cell hyperplasia in all dosed groups of males and females were significantly greater than those in the vehicle control groups.

GENETIC TOXICOLOGY

Coconut oil acid diethanolamine condensate did not show genotoxic activity *in vitro*. It was not mutagenic in *Salmonella typhimurium*, nor did it produce an increase in mutant L5178Y mouse lymphoma cell colonies. In addition, no increases in the frequencies of sister chromatid exchanges or chromosomal aberrations were observed in Chinese hamster ovary cells after incubation with coconut oil acid diethanolamine condensate. All these *in vitro* assays were conducted with and without induced S9 activation enzymes. In contrast to the uniformly negative results *in vitro*, positive results were obtained in a peripheral blood micronucleus test in male and female mice from the 14-week dermal study.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of coconut oil acid diethanolamine condensate in male F344/N rats administered 50 or 100 mg/kg. There was *equivocal evidence of carcinogenic activity* in female F344/N rats based on a marginal increase in the incidences of renal tubule neoplasms. There was *clear evidence of carcinogenic activity* in male $B6C3F_1$ mice based on increased incidences of hepatic and renal tubule neoplasms and in female $B6C3F_1$ mice based on increased incidences of hepatic neoplasms. These increases were associated with the concentration of free diethanolamine present as a contaminant in the diethanolamine condensate.

Exposure of rats to coconut oil acid diethanolamine condensate by dermal application in ethanol for 2 years resulted in epidermal hyperplasia, sebaceous gland hyperplasia, hyperkeratosis, and parakeratosis in males and females and ulcer in females at the site of application. There were increases in the incidences of chronic inflammation, epithelial hyperplasia, and epithelial ulcer in the forestomach of female rats. The severities of nephropathy in dosed female rats were increased.

Exposure of mice to coconut oil acid diethanolamine condensate by dermal application for 2 years resulted in increased incidences of eosinophilic foci of the liver in males. Increased incidences of epidermal hyperplasia, sebaceous gland hyperplasia, and hyperkeratosis in males and females, ulcer in males, and parakeratosis and inflammation in females at the site of application and of follicular cell hyperplasia in the thyroid gland of males and females were chemical related.

---

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Coconut Oil Acid Diethanolamine Condensate

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses in ethanol by dermal application	Vehicle control, 50, or 100 mg/kg	Vehicle control, 50, or 100 mg/kg	Vehicle control, 100, or 200 mg/kg	Vehicle control, 100, or 200 mg/kg
Body weights	Dosed groups similar to vehicle controls	Dosed groups similar to vehicle controls	Dosed groups similar to vehicle controls	Dosed groups less than vehicle controls
Survival rates	8/50, 12/50, 11/50	28/50, 24/50, 22/50	41/50, 37/50, 36/50	35/50, 36/50, 26/50
Nonneoplastic effects	Skin, site of application: epidermal hyperplasia (0/50, 46/50, 50/50); sebaceous gland hyperplasia (0/50, 45/50, 50/50); parakeratosis (0/50, 9/50, 28/50); hyperkeratosis (0/50, 36/50, 48/50);	Skin, site of application: epidermal hyperplasia (3/50, 46/50, 50/50); sebaceous gland hyperplasia (2/50, 46/50, 49/50); parakeratosis (1/50, 11/50, 23/50); hyperkeratosis (3/50, 45/50, 47/50); ulcer (2/50, 0/50, 9/50) Forestomach: chronic active inflammation (1/50, 3/50, 10/50); epithelial hyperplasia (2/50, 5/50, 13/50); epithelial ulcer (1/50, 3/50, 11/50) Kidney: severity of nephropathy (1.6, 2.1, 2.7)	Liver: eosinophilic foci (20/50, 29/50, 31/50) Skin, site of application: epidermal hyperplasia (5/50, 47/50, 50/50); sebaceous gland hyperplasia (0/50, 44/50, 49/50); hyperkeratosis (0/50, 24/50, 23/50); ulcer (1/50, 0/50, 7/50) Thyroid gland: follicular cell hyperplasia (11/50, 20/50, 23/50)	Skin, site of application: epidermal hyperplasia (9/50, 47/50, 50/50); sebaceous gland hyperplasia (0/50, 42/50, 48/50); hyperkeratosis (5/50, 30/50, 40/50); chronic active inflammation (3/50, 2/50, 11/50); parakeratosis (3/50, 4/50, 16/50) Thyroid gland: follicular cell hyperplasia (27/50, 36/50, 33/50)
Neoplastic effects	None	None	Liver: hepatocellular adenoma (22/50, 35/50, 45/50); hepatoblastoma (1/50, 1/50, 10/50); hepatocellular adenoma, carcinoma, or hepatoblastoma (29/50, 39/50, 49/50) Kidney: renal tubule adenoma (1/50, 1/50, 7/50); renal tubule adenoma or carcinoma (1/50, 1/50, 9/50)	Liver: hepatocellular adenoma (32/50, 44/50, 43/50); hepatocellular carcinoma (3/50, 21/50, 32/50); hepatocellular adenoma, carcinoma, or hepatoblastoma (33/50, 46/50, 48/50)
Uncertain findings	None	Kidney: renal tubule adenoma or carcinoma (standard evaluation - 0/50, 2/50, 0/50 ; standard and extended evaluations combined - 0/50, 4/50, 1/50)	None	None

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Coconut Oil Acid Diethanolamine Condensate

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Level of evidence of carcinogenic activity	No evidence	Equivocal evidence	Clear evidence	Clear evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:		Negative in strains TA97, TA98, TA100, and TA1535		
Mouse lymphoma gene mutations:		Negative with or without S9		
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro:*		Negative with or without S9		
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:		Negative with or without S9		
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo*:		Positive in males and females		

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on coconut oil acid diethanolamine condensate on 9 December 1997 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

Gary P. Carlson, Ph.D., Chairperson
School of Health Sciences
Purdue University
West Lafayette, IN

A. John Bailer, Ph.D.
Department of Mathematics and Statistics
Miami University
Oxford, OH

Steven A. Belinsky, Ph.D.
Inhalation Toxicology Research Institute
Kirkland Air Force Base
Albuquerque, NM

James S. Bus, Ph.D.
Health and Environmental Sciences
Dow Chemical Company
Midland, MI

Linda A. Chatman, D.V.M.
Pfizer, Inc.
Groton, CT

John M. Cullen, Ph.D., V.M.D.
Department of Microbiology, Parasitology, and Pathology
College of Veterinary Medicine
North Carolina State University
Raleigh, NC

Susan M. Fischer, Ph.D.
M.D. Anderson Cancer Center
University of Texas
Smithville, TX

Thomas L. Goldsworthy, Ph.D., Principal Reviewer
Integrated Laboratory Systems
Research Triangle Park, NC

Irma Russo, M.D., Principal Reviewer
Fox Chase Cancer Center
Philadelphia, PA

Special Reviewers

Stephen S. Hecht, Ph.D., Principal Reviewer
University of Minnesota Cancer Centers
Minneapolis, MN

Michele Medinsky, Ph.D.
Chemical Industry Institute of Toxicology
Research Triangle Park, NC

Jose Russo, M.D.
Fox Chase Cancer Center
Philadelphia, PA

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 9 December 1997, the draft Technical Report on the toxicology and carcinogenesis studies of coconut oil acid diethanolamine condensate received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of coconut oil acid diethanolamine condensate by discussing the uses of the chemical and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplastic and nonneoplastic lesions in rats and mice. The proposed conclusions were *no evidence of carcinogenic activity* in male F344/N rats, *equivocal evidence of carcinogenic activity* in female F344/N rats, and *clear evidence of carcinogenic activity* in male and female B6C3F$_1$ mice.

Dr. Irwin discussed a logistic regression model designed to quantitatively evaluate the association between hepatocellular neoplasms in female mice and free diethanolamine concentration. He said that this model tended to strengthen the hypothesis that increased incidences of hepatocellular neoplasms in mice are associated with diethanolamine exposure. This model was also applied to the other two diethanolamine condensates tested.

Dr. I. Russo, the first principal reviewer, agreed with the proposed conclusions. She questioned the use of ethanol as the solvent, because coconut oil acid diethanolamine condensate is water soluble. Dr. Irwin responded that the primary purpose for using ethanol as the solvent was to allow comparison of results from all three of the diethanolamides, the other two of which are not water soluble. Furthermore, when water is used as the solvent in dermal studies, the solutions tend to become beaded and do not spread well.

Dr. Goldsworthy, the second principal reviewer, agreed with the proposed conclusions. However, he argued that the statement attributing all the neoplasm responses to free diethanolamine does not appear warranted because the association is mainly supported by data for female mice, while there are gaps of information and a lack of definitive conclusions for the liver as well as for other neoplasm sites. He said that correlations were not assessed for liver neoplasms in male mice. Furthermore, the link between hepatic neoplasm formation and concentrations of free diethanolamine clearly does not apply to hepatoblastoma occurrence. Dr. Irwin agreed that there may be other neoplastic responses not associated with diethanolamine.

Dr. Hecht, the third principal reviewer, agreed with the proposed conclusions. He said that it would have been more satisfactory to have tested the diethanolamides in the absence of diethanolamine, although he realized that the strategy was to test the product as it actually is used. Dr. J.R. Bucher, NIEHS, agreed but stated that because this is a safety assessment issue, the determining factor was the diethanolamide as it is used in cosmetics. Dr. Hecht asked for some discussion of the significance of the liver neoplasms in a strain of mouse that already has a considerable spontaneous incidence of such neoplasms. Spontaneous incidences, along with the fact that no other substantial neoplasm responses were observed, suggest that coconut oil acid diethanolamine condensate is a weak carcinogen.

Dr. L. Loretz, The Cosmetic, Toiletry, and Fragrance Association (CTFA), said that there was inadequate documentation and analysis of the test materials, particularly when attributing neoplasm effects of the condensates to diethanolamine content. Furthermore, the test animals appeared to have ingested some of the material, and the inappropriate use of ethanol as the vehicle complicated interpretation of study results in that The International Agency for Research on Cancer (IARC) lists ethanol in beverages as a known human carcinogen. Finally, Dr. Loretz asked that the level of evidence for male mice, which was based on kidney neoplasms, be changed from *clear* to *some evidence of carcinogenic activity* because the response was limited to one species, one gender, and one dose and consisted primarily of benign neoplasms.

Dr. I. Russo moved that the Technical Report on coconut oil acid diethanolamine condensate be accepted with the revisions discussed and the conclusions as written with the addition of the word "marginal" before "increased" in the conclusion for female rats. Dr. Fischer seconded the motion. Dr. Goldsworthy moved that the motion be amended such that the last sentence of the conclusions for carcinogenicity be changed from "These increases were attributed to the concentration of free diethanolamine present as a contaminant" to "These increases were associated with the concentration of free diethanolamine present as a contaminant." Dr. Belinsky seconded the amendment, which was accepted by seven yes votes and one abstention (Dr. Bus). The amended motion was then accepted by seven yes votes and one abstention (Dr. Bus).